

## CASE REPORT

# Cutaneous manifestations of thyroid cancer: a report of four cases and review of the literature

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Cutaneous metastases from thyroid carcinoma are rare. This report describes four cases of thyroid carcinoma metastatic to the skin. Two cases were medullary carcinoma and two were papillary thyroid carcinoma. In two cases, skin metastases were the presenting feature of the underlying thyroid carcinoma. Examination of the skin lesions by conventional light microscopy suggested the possibility of metastatic carcinoma and immunohistochemical tests confirmed the diagnosis. Subsequent investigations identified primary thyroid lesions. In two cases, the skin metastasis was the first evidence of the recurrence of known thyroid carcinoma. These cases identify a novel presentation of thyroid carcinoma.

Thyroid carcinoma is the most common endocrine malignancy. It usually presents as a thyroid nodule, but occasionally patients manifest with unusual features. The presence of metastatic disease at the time of diagnosis is a bad prognostic feature, and patients who present with symptomatic metastases do very poorly.<sup>1–4</sup>

Carcinomas derived from follicular epithelial cells include papillary and follicular carcinoma, poorly differentiated carcinoma (also known as “insular” carcinoma), and anaplastic carcinoma. Papillary carcinoma is the most common of these in North America. The most common site of metastasis is to lymph nodes in the neck.<sup>3,4</sup> Rarely, papillary and follicular carcinomas spread haematogenously, involving lung, liver, bone, and occasionally brain.<sup>5–11</sup>

Medullary carcinomas of the thyroid are neuroendocrine neoplasms originating from the parafollicular cells or C cells. These lesions also metastasise to locoregional lymph nodes, and spread haematogenously to affect liver and lungs.<sup>12,13</sup>

Anaplastic thyroid carcinoma is a rare and aggressive tumour that can metastasise to the skin in the context of diffuse body metastases.<sup>14</sup> By contrast, cutaneous metastasis from differentiated thyroid carcinoma is a rare manifestation of disseminated disease. Some authors believe that follicular carcinoma of the thyroid has a higher propensity to metastasise to the skin, followed by papillary carcinoma, then anaplastic carcinoma, and finally medullary carcinoma.<sup>3</sup> Others believe that papillary carcinoma is the most common thyroid carcinoma metastasising to the skin.<sup>4</sup> All agree that the scalp is the most common site of thyroid carcinoma skin metastases. The metastatic deposits usually present as flesh coloured nodules that are tender, may be itchy, and can ulcerate. Skin metastasis from a thyroid carcinoma is rarely a presenting feature of an underlying malignancy.<sup>1,2</sup> The average length of survival after cutaneous metastasis is 19 months, because it usually occurs in the context of disseminated neoplastic disease.<sup>4</sup>

“Skin metastasis from a thyroid carcinoma is rarely a presenting feature of an underlying malignancy”

We report four recent cases in which patients presented with metastatic thyroid carcinoma to the skin. In two of these patients, the skin lesions were the initial manifestation of thyroid cancer, and in the other two they indicated systemic spread of known cancer. In all patients, the diagnosis was not suspected clinically, and the pathology brought to our attention the importance of thyroid carcinoma in the differential diagnosis of atypical skin lesions.

## CASE REPORTS

### Case 1

A 46 year old man with no family history of thyroid or other endocrine diseases presented with an enlarging tender scalp lesion. It was resected with a clinical diagnosis of an adnexal tumour. Histological examination identified an infiltrating carcinoma composed of nests and cords of small spindle shaped and irregular cells, with prominent hyperchromatic nuclei and scant cytoplasm. There was no involvement of the epidermis because the lesion was limited to the dermal component. Immunohistochemical studies revealed strong positivity for chromogranin and calcitonin. Amyloid stains were negative.

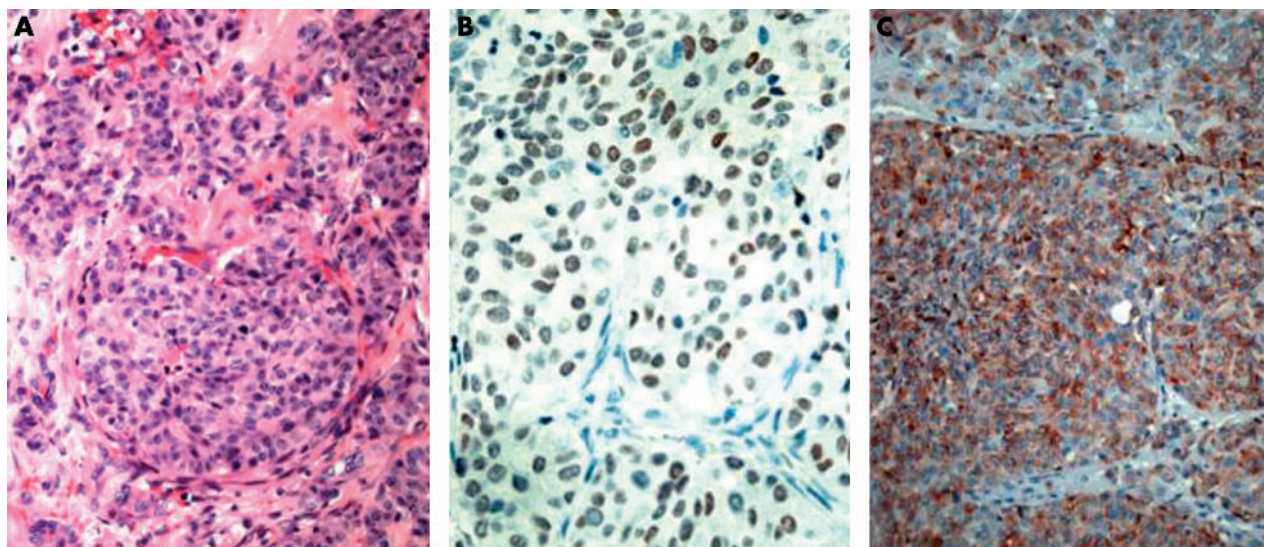
During investigations, the patient complained of neck pain and a thyroid mass was palpated. Two needle biopsies were inconclusive, but in light of the scalp lesion, the presumptive diagnosis was medullary thyroid carcinoma and the patient underwent total thyroidectomy. The surgical resection was difficult because of extensive extrathyroidal tumour infiltration. Examination of the thyroidectomy specimen showed a 5 cm tumour and, despite the previously extensive local infiltration, no jugular or central lymphadenopathy was found intraoperatively. On microscopic examination, vascular space invasion was identified and micrometastatic disease was found in four perithyroidal lymph nodes. The tumour had the same histology and immunohistochemical staining pattern as the previous skin biopsy. The patient went on to develop metastatic disease in bone, jugular lymph nodes, and the lung. He was treated with palliative external beam irradiation for pain control.

### Case 2

A 34 year old man presented with tender scalp nodules, chest wall nodules, and sore ribs. One of the chest wall nodules was excised and submitted for histopathological examination.

The lesion was composed of nests of cohesive malignant cells within fibroadipose tissue. The cells were predominantly epithelioid, but in some areas they had spindle shaped

**Abbreviations:** TTF-1, thyroid transcription factor 1



**Figure 1** Medullary thyroid carcinoma metastatic to the skin (case 2). (A) The skin tumour is composed of epithelioid and spindle cells arranged in nests, characteristic of a neuroendocrine tumour (haematoxylin and eosin stain). (B) The tumour cells contain intense nuclear reactivity for TTF-1, a transcription factor that indicates thyroid or lung derivation. (C) Immunopositivity for cytoplasmic chromogranin confirms neuroendocrine differentiation.

morphology (fig 1A). They contained a moderate amount of amphophilic cytoplasm with irregular, hyperchromatic nuclei containing prominent nucleoli. Necrosis was present focally and mitoses were identified. The tumour was negative with the periodic acid Schiff and mucicarmine stains for mucin, which is present in many adenocarcinomas, but not thyroid cancer. Immunoperoxidase staining showed positivity for keratins with the AE1/AE3 antibodies and anticytokeratin 7 antibodies. The tumour was also positive for thyroid transcription factor 1 (TTF-1), which is found in epithelium derived from thyroid and lung (fig 1B). The tumour was immunopositive for synaptophysin, CD56, and chromogranin (fig 1C)—markers of cells with a neuroendocrine derivation—and was also positive for carcinoembryonic antigen, a non-specific marker of visceral malignancy, which in the thyroid is expressed only in medullary carcinomas. It was also reactive for calcitonin but was negative for amyloid and thyroglobulin. The tumour was negative for high molecular weight keratins and cytokeratin 20, markers of gastrointestinal carcinomas, which are usually negative in thyroid cancers. The tumour cells were also negative for S-100 protein and did not react with HMB-45, thus ruling out the diagnosis of melanoma. Calretinin, which is highly specific for mesothelioma, and placental alkaline phosphatase, which stains seminoma, were both negative. The findings were consistent with a medullary carcinoma of the thyroid.

The patient was investigated and was found to have a 1.6 cm nodule in the left thyroid lobe. The nodule was biopsied and medullary carcinoma was confirmed. Imaging revealed bony and liver metastases. Despite these findings the patient was and remains totally asymptomatic. His calcitonin concentration was 251 ng/litre and remained unchanged after chemotherapy and palliative radiotherapy. The size of some of the skin nodules was reduced by about 50% after chemotherapy.

### Case 3

A 71 year old woman presented with a growing, flesh coloured nodule of the parietal scalp. The concern of the treating physician at that time was to rule out a cyst or adnexal tumour. A biopsy was performed. On histological

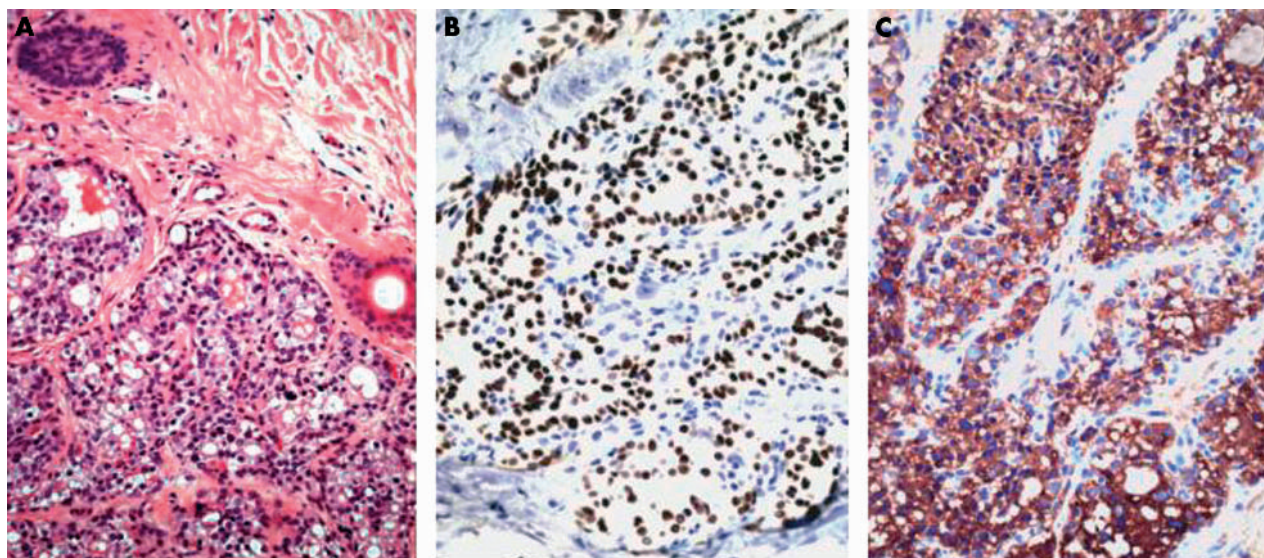
examination, the lesion was composed of an epithelial tumour involving dermis and subcutaneous tissue (fig 2A). It was lobulated and consisted of atypical glandular cells forming follicular structures containing colloid-like material. The tumour cells had large nuclei and prominent nucleoli, nuclear grooves, and occasional intranuclear inclusions. Immunohistochemical analysis showed positivity for vimentin, low molecular weight cytokeratins, and cytokeratin 7. There was strong nuclear TTF-1 reactivity (fig 2B) and cytoplasmic thyroglobulin staining (fig 2C). The tumour was negative for smooth muscle actin and muscle specific actin—thereby excluding a sarcoma—and was also negative for high molecular weight keratins, cytokeratin 20, and S100 protein. Staining for carcinoembryonic antigen and epithelial membrane antigen did not reveal tubular adnexal structural formations. The features were consistent with metastatic papillary thyroid carcinoma.

The patient had a history of a thyroidectomy six years previously. This had revealed a follicular variant papillary carcinoma that exhibited vascular and lymphatic invasion. The patient refused I<sup>131</sup> treatment at that time. One year after thyroidectomy, the patient had evidence of lung and skeletal metastases and she was treated with radioactive iodine at a dose of 400 mCi, which resulted in total radiological regression of the lesions. She remained clinically asymptomatic on follow up until this skin lesion developed. After the diagnosis of metastatic papillary carcinoma of the thyroid in this skin lesion, she underwent further investigations that identified a recurrence of lung metastases and new liver metastases. She was offered radioactive iodine at 200 mCi and palliative external beam radiotherapy. The patient's condition deteriorated after the first treatment with iodine and she developed haemoptysis and shortness of breath. The patient refused further treatment.

### Case 4

An 82 year old woman presented with a 4 cm, dark, painless nodule on the neck. The clinical impression was of an atypical naevus and the lesion was resected. Histological examination revealed a cystic lesion in the dermis filled with complex papillary structures. These were lined by tall columnar





**Figure 2** Papillary thyroid carcinoma metastatic to skin (case 3). (A) This skin tumour is composed of tubules containing colloid-like material and lined by cells with nuclear grooves. The features are those of papillary thyroid carcinoma. (B) The tumour cells exhibit strong nuclear staining for TTF-1, a transcription factor that indicates thyroid or lung derivation. (C) The diagnosis of metastatic thyroid carcinoma is confirmed by cytoplasmic staining for thyroglobulin.

epithelial cells, with moderately enlarged nuclei that contained irregular nuclear contours with grooves and cytoplasmic pseudoinclusions. Immunohistochemistry identified strong nuclear TTF-1 reactivity and focal cytoplasmic thyroglobulin staining. The features were those of metastatic papillary thyroid carcinoma.

The patient had a history of a total thyroidectomy 11 years previously. The pathology at that time revealed papillary carcinoma with focal extrathyroidal extension into skeletal muscle. The resection margins were free of malignancy and there was no evidence of metastatic disease. She refused treatment with radioactive iodine and remained asymptomatic for 11 years. At this time, she has no other evidence of disseminated disease and is completely asymptomatic.

## DISCUSSION

Cutaneous metastasis from thyroid carcinoma is rare. It usually occurs in the setting of disseminated neoplastic disease.<sup>1-4</sup> Dahl *et al* reviewed the English literature from 1964 onwards and found 43 cases of thyroid carcinoma with skin metastases. They found that papillary carcinoma was the most common thyroid cancer to result in skin metastases, representing 41% of cases, followed by follicular carcinoma at 28%, with anaplastic carcinoma and medullary carcinoma each contributing 15% of cases. The scalp was the most common site of involvement.<sup>4</sup> In contrast, Koller *et al* reported that follicular carcinoma has a greater preponderance than papillary carcinoma for cutaneous metastases. The condition is equally as common in men and women.<sup>3</sup> As in our patients, occasionally skin metastases represent the initial manifestation of an occult thyroid carcinoma.

“Clinically, the investigation of a flesh coloured skin nodule, particularly in the scalp area, should include the possibility of metastatic thyroid carcinoma”

Metastatic thyroid carcinoma involving the skin can easily be mistaken for a primary adnexal skin tumour. The correct diagnosis requires a high index of suspicion and the liberal use of immunohistochemical stains. The development of antibodies against the thyroid transcription factor TTF-1 has

provided a useful tool to screen for metastatic carcinomas. TTF-1 is a 38 kDa homeodomain containing, DNA binding protein, originally identified in follicular cells of the thyroid and subsequently in pneumocytes and thyroid C cells. Anti-TTF-1 antibodies have proved very useful in distinguishing pulmonary and thyroid carcinoma from other primary carcinomas or mesothelioma, and in distinguishing metastatic small cell carcinoma of the lung from primary cutaneous Merkel cell carcinoma. They may also be useful in distinguishing neuroendocrine tumours of the lung from well differentiated neuroendocrine tumours from other sites, such as the gut and pancreas.<sup>15-17</sup> Thyroglobulin expression identifies carcinomas of thyroid follicular cell derivation, including both papillary and follicular types, but is not found in lung carcinomas.<sup>18</sup> Medullary carcinomas are readily identified by neuroendocrine markers, including synaptophysin, chromogranin, and CD56, in addition to the specific tumour marker of this entity, calcitonin.

Clinically, the investigation of a flesh coloured skin nodule, particularly in the scalp area, should include the possibility of metastatic thyroid carcinoma. This is most important when the patient has a history of thyroid cancer but, as in two of our patients, biopsy of such lesions may lead to the detection of occult thyroid carcinoma.

## Take home messages

- We describe four rare cases of thyroid carcinoma metastatic to the skin
- In two cases, the skin metastases were the presenting feature of the underlying thyroid carcinoma and in the other two cases the skin metastasis was the first evidence of the recurrence of known thyroid carcinoma
- These cases identify a novel presentation of thyroid carcinoma and highlight the importance of thyroid carcinoma in the differential diagnosis of atypical skin lesions

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